

applying both said tropoelastin and said lysyl oxidase to a skin wound simultaneously or sequentially, so that said tropoelastin is not cross-linked to itself prior to application to the wound.

13. (Twice amended) A kit comprising tropoelastin substantially identical to wild type tropoelastin, wherein the tropoelastin has not previously been cross-linked and is therefore available for cross-linking, and lysyl oxidase substantially identical to wild type lysyl oxidase in separate compartments.

### Remarks

Claims 1, 2, 5, 9-14, and 17 are pending in the application. Claims 1, 2, 5, 9-14, and 17 stand rejected. Claims 1 and 13 have been amended. Support for the amendment can be found in the Specification at page 19, lines 13-14. No new matter is added to the application by this Amendment. Applicant respectfully requests reexamination and reconsideration of the case. Each of the rejections levied in the Office Action is addressed individually below.

I. Rejection under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Weiss, WO 98/06830. Claims 1, 2, 5, 11-14, and 17 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Weiss (WO 98/06830). Examiner states that Weiss teaches that lysyl oxidase and its non-crosslinked substrate, tropoelastin, are simultaneously applied to a wound where the tropoelastin is within a matrix. Applicant submits that Weiss does not anticipate or render obvious the claimed invention as amended herein because the tropoelastin is provided in a matrix implying that the tropoelastin is crosslinked. The tropoelastin in a matrix including other extracellular matrix proteins such as elastin and collagen, as taught by Weiss, would be cross-linked and would not be available for further cross-linking as claimed in the present Application. The claimed invention uses virgin tropoelastin that has been prepared recombinantly. Therefore, the tropoelastin used in the claimed method has never been cross-linked and is fully available for cross-linking when it is applied to the wound along with lysyl oxidase. The use of this form of tropoelastin has the advantage of being able to readily crosslink itself into the extracellular matrix already present at the wound site.

With regard to the alternative obviousness rejection, Applicant would like to point out that Weiss has not appreciated the advantage of using non-crosslinked tropoelastin and applying it to a wound simultaneously with lysyl oxidase to promote wound healing. Weiss does not teach or even suggest using non-crosslinked tropoelastin in his disclosure; therefore, the claims cannot be anticipated or rendered obvious by the claimed invention.

Clearly, Weiss does not contemplate the claimed invention in which lysyl oxidase and virgin non-crosslinked tropoelastin are maintained separate from one another until being applied to a wound. Applicant, therefore, submits that Weiss cannot anticipate or render obvious the claimed invention and requests that the rejections be removed.

**II. Rejection under 35 U.S.C. § 103, as obvious over Weiss, U.S. Patent 6,277,622, in view of Kagan, in Regulation of Matrix Accumulation, 1986.** Claim 9 stands rejected under 35 U.S.C. § 103 as obvious over Weiss (U.S. Patent 6,277,622) in view of Kagan, in *Regulation of Matrix Accumulation*, pp. 321-3988, 1986. Examiner submits that it would have been readily recognized by one of skill in the art that the lysyl oxidase applied at any particular time to the wound may suffer a loss of activity at the wound site where a decrease in the levels of copper ion in the body would reduce the activity of the previously applied enzyme requiring its replenishment. First, Applicant submits that claim 9 is not rendered obvious by the cited references because neither reference, even when combined, even teaches the one-time application of a tropoelastin, which has not been previously crosslinked and therefore is available for crosslinking, as discussed above. The Kagan reference does not make up for this deficiency in the Weiss patent; therefore, these combined references do not render obvious the repeated administration of lysyl oxidase and tropoelastin.

In addition, regarding repeated administration as recited in claim 9, any application of the lysyl oxidase enzyme would include the necessary cofactors for oxidase activity. There would be no loss of lysyl oxidase activity at the wound site due to a decrease in the levels of copper in the body. Most enzymes requiring metal ion cofactors have the metal tightly bound so that the metal ion does not leach out from the enzyme even in an environment with a very low metal ion concentration. Therefore, Kagan provides no incentive for one of skill in the art to provide multiple applications.

The claimed invention is not rendered obvious due to these two substantial differences between the claimed invention and the cited art. Applicant requests that the rejection be removed.

**III. Rejection under 35 U.S.C. § 103, as obvious over Weiss, U.S. Patent 6,277,622, in view of Khadem et al., U.S. Patent 5,552,452.** Claim 10 stands rejected under 35 U.S.C. § 103 as obvious over Weiss (U.S. Patent 6,277,622) in view of Khadem *et al.* (U.S. Patent 5,552,452). Examiner states that it would have been obvious to one of ordinary skill in the art to use sutures, staples, adhesive strips, or tissue glue, as taught by Khadem *et al.*, to approximate separated wound tissues and apply lysyl oxidase and tropoelastin. Applicant submits that claim 10 is not rendered obvious by the cited references because neither reference, even when combined, teaches or even suggests the application of a tropoelastin not previously crosslinked and therefore available for crosslinking, as discussed above. The reference by Khadem *et al.* does not make up for this deficiency in the Weiss patent. Therefore, Applicant requests that the rejection be removed.

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

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Respectfully submitted,



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